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Advances in the Treatment of Acute ITP

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ABSTRACT

Immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenic purpura, is a hematologic disease in which platelet destruction increases and production decreases, mainly mediated by immunity. However, up to now, the pathogenesis of ITP is not clear, which has caused great trouble in treatment. Therefore, this paper intends to review the recent literature on ITP treatment to provide some reference for clinical treatment. This paper combines the evidence of ASH immune thrombocytopenia and the Chinese Guidelines for the Diagnosis and Treatment of Adult primary immune thrombocytopenia (2020 edition). In this paper, the treatment process of ITP was divided into first-line treatment and second-line treatment, and it was concluded that first-line treatment was often used when newly diagnosed with ITP: combination of high-dose dexamethasone and low-dose gamma globulin. However, it should be noted that only 60%-80% of patients responded to first-line treatment, and most of them relapsed during dosing reduction or drug withdrawal. Second-line treatment is recommended in this case. The standard treatment is splenectomy, but due to its uncontrollable nature and side effects, it should be used cautiously. A new treatment approach, thrombogenin receptor agonist, has great development potential, and multidrug combination therapy for ITP has positive clinical significance.

1. Introduction

Immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenia purpura, is a hematologic disease with increased platelet destruction and reduced production, mainly mediated by immunity. ITP is mainly manifested as isolated thrombocytopenia (platelet count < 100×109/L) accompanied by clinical symptoms of skin and mucosal bleeding. ITP can affect people of all ages, but mainly occurs in children, women of childbearing age and the elderly. Its pathogenesis is complex, involving multiple processes of humoral immunity and cellular immunity, and its clinical treatment is difficult. In this review, we will review the current progress in the treatment of ITP based on the evidence-based guidelines for ASH immune thrombocytopenia, the Chinese Guidelines for the Diagnosis and Treatment of Adult Primary immune thrombocytopenia (2020 edition) and

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recent major studies.

2. First-line Treatment

2.1 Hormone Therapy

For newly diagnosed ITP, patients with platelet count < 30×10^9 /L are generally recommended to be treated with glucocorticoids [1]. Meanwhile, *Chinese Guidelines for the Diagnosis and Treatment of Adult Primary Immune thrombocytopenia* (2020 Edition) indicated that high-dose dexamethasone (HD-DXM) 40mg/d×4d, oral or intravenous administration, and patients with ineffective or recurrent disease could repeat one cycle. During treatment, blood pressure and blood glucose levels should be monitored to prevent infection and gastrointestinal ulcer [2].

Large-dose DXM is the first choice in clinical practice, and its effect is mainly reflected in the negative regulation of the combination of antibody and autoantibody formation, inhibition of C3b and Fc receptor function, and reduction of platelet phagocytosis due to monocyte macrophage system. Reduce destruction and increase generation [3].

In addition, XM single drug treatment of ITP can rapidly improve PLT level, with significant efficacy within 30 days [4]. Wang Xiaojun et al. treated 26 ITP patients who had not received other treatment before hospital only with high-dose dexamethasone therapy, acid inhibition, gastric mucosa protection and other adjuvant treatments, and the results showed that 18 cases (69.23%) of the 26 cases were significantly effective, 3 cases (11.54%) were effective, and 2 cases (7.69%) were improved within two weeks. The total effective rate was 88.46% [4,5]. However, long-term clinical data analysis showed that the treatment with large dose OF DXM alone could not achieve satisfactory efficacy, and patients were prone to relapse or even refractory ITP [5]. Research shows that DXM combination therapy effect is DXM monotherapy effect significantly increased, in recent years, DXM combination treatment of ITP has become many scholars study the direction of the common combination of IVIg, ai QuBo palmer ethanolamine, etc., to the later several drug treatment mechanism and treatment effects were discussed.

2.2 IVIg Treatment

Gamma globulin (HD-IVIG) is a preparation rich in immunoglobulin, which has antiviral, antibacterial and antitoxin effects and can also enhance human immunity. It is often used in the treatment of ITP combined with glucocorticoid at the present stage. Numerous studies have pointed out that: Gamma globulin can effectively prevent thrombocytopenic purpura with antiplatelet antibodies, blocking antibody and platelet, and mononuclear cells and macrophage phagocytosis of platelets, [9] clinically often associated with glucocorticoid (such as dexamethasone, methyl prednisolone steroids) combination, to achieve the purpose of the treatment of ITP, 50 ITP patients were randomly divided into control group (25 cases) and treatment group (25 cases) through controlled experiment. The control group was only given standard treatment of glucocorticoid regimen, and the experimental group was given intravenous infusion of IVIg400mg/kg· D-1 on the basis of this treatment, and the total effective rate was 76% in the control group and 92% in the treatment group for 5 days. It can be seen that the combined treatment effect is obvious [10,11].

It is worth noting that the cost of gamma globulin is high, and the massive use will undoubtedly increase the economic burden of patients. Recent studies mainly focus on the effect of the dosage of gamma globulin on the therapeutic effect when DXM is combined with gamma globulin. Data show that when IVIG is used in the treatment of ITP with low dose and normal dose. Differences in platelet parameters and efficacy were not statistically significant [11,12], so low-dose IVIG can be considered for clinical treatment.

3. Second-line Treatment

3.1 Splenectomy

Second-line treatment is recommended for patients with ITP ≥3 months and corticosteroid dependence or no response [1]. Splenectomy is one of the standard treatments of second-line therapy. The spleen is the largest lymphatic organ in the human body and an important site for antibody production, antigen presentation and the persistence of autoimmune responses [26]. Splenectomy plays a clinical role in the treatment of ITP mainly by removing platelet destruction and some important parts of anti-platelet antibody production [27]. Splenectomy at this stage can be divided into Open splenectomy (splenectomy, splenectomy,OS) and laparoscopic splenectomy (aparoscopic splenectomy, LS). At the same time, COMPARED with the former, LS has the characteristics of smaller postoperative wounds and faster recovery of patients. The main limitation of LS is splenomegaly (spleen weight over 500 g), but it is worth noting that laparoscopic splenectomy can also be considered as a treatment plan even in the case of extreme

splenomegaly (spleen weight over 2000g) [29]. Therefore, splenomegaly that causes technical difficulties is not characteristic of ITP. Several clinical trials have observed that LS has excellent efficacy for ITP patients. Liao Rui [28] used LS to treat clinically refractory ITP patients, and the results showed that 65 of the 78 patients (83.3%) had stable remission after LS, without further treatment of ITP. Ducassou Stephane [13] conducted an experimental study on 137 ITP patients using four second-line treatment approaches (splenectomy, hydroxychloroquine, azathioprine and rituximab), and the results showed that the cure rate of all patients was 62% after 24 months, among which the cure rate of 56 patients who underwent splenectomy was 85%. The cure rate was 60% for 23 patients on hydroxychloroquine, 46% for 24 patients on azathioprine, and 37% for 34 patients on rituximab. Therefore, splenectomy is still an effective way to treat ITP.

However, it is worth mentioning that splenectomy has the risks of intraoperative splenic artery hemorrhage, thrombosis, damage to pancreas and tail of pancreas, resulting in local pancreatic fistula, local abscess formation, infection and other complications [14,15]. Therefore, considering the trauma, irreversibility, and unpredictability of splenectomy, traditional open splenectomy should be used with caution if drug therapy fails [16]. According to previous international consensus reports, splenectomy should be performed 12 to 24 months after the diagnosis of ITP, when patients still have a high probability of recovery [17]. At the same time there are constantly new clinical data showed that compared with traditional open surgery, laparoscopic splenectomy, as a kind of minimally invasive surgery with small trauma, rapid recovery, low infection rate of significant advantages to become the gold standard for surgical treatment of ITP [30], given the recent research has shown that preoperative platelet amount is not the absolute contraindication of laparoscopic splenectomy [31]. As well as the development of endoscopic technology, the improvement of surgical techniques and the increase of clinical experience, more and more clinicians advocate advancing the schedule of LS surgery for ITP patients, so as to reduce the complications caused by hormone therapy (such as obesity), so as to improve surgical safety and postoperative efficacy [31].

3.2 Thrombopoietin Receptor Agonist (TPO-RA)

Thromboietin receptor agonists (TPO-RA) are a newly emerging drug for the treatment of ITP in recent years. ASH guidelines suggest that TPO receptor agonists are preferred when patients want to avoid surgery and achieve lasting remission [1]. Currently, new TPO-RA products that have passed clinical trials and been approved for marketing include Altrepopal, romistine, lusantrepopal and Avantrepopal [18]. Among them, altrepopa and romistine are the most widely used in clinical application. Romistine is an Fc fusion protein attached with four 14-amino acid TPO peptides (peptidomes), which stimulate TPO receptors by binding to the extracytoplasmic domain (extracytoplasmic domain similar to endogenous TPO) [33]. Aitrippa is an orally taken non-peptide TPO-R agonist, which is structurally independent of eTPO and selectively interacts with TPO-R rather than competing with TPO.

This results in increased proliferation and differentiation of bone marrow progenitor cells into megakaryocytes and increased platelet production [34]. TPO-RA can restore the balance of FcγR by up-regulating the expression of inhibitory FcγRIIb, thereby reducing the activity of FcγR mediated monocytes/macrophages, and thus achieving the effects of continuous treatment on ITP, such as stimulating and regulating B cells and T lymphocytes, reconstructing immune tolerance and reducing inflammatory response [21,32], TPO-RA can also reduce hematopoietic stem/progenitor cell apoptosis, improve DNA damage repair, and protect and maintain its hematopoietic function [22]. The commonly used doses of romistine and attribopa are 1-10μg/ (kg·w) and 25-75 mg/d, respectively, which should be adjusted at any time according to the number of peripheral blood plates of patients, so that the number of peripheral blood plates of patients can be stabilized at (50-200) ×109 /L [17]. The platelet response rate of patients after treatment can reach 50%-90%, and it is well tolerated after long-term use, and the myeloid reticular fibrosis in a few patients can be reversed even after the termination of treatment [35]. A large number of recent studies have shown the possibility of sustained remission in ITP patients after tPO-RA discontinuation. Although it is not clear which type of patients can achieve sustained remission and how to stop TPO-RA, evidence of sustained remission in ITP patients after TPO-RA discontinuation is still increasing. This may change the traditional treatment model that some patients need long-term maintenance therapy [23].

4. Prospect of Combined TCM and Western Medicine Therapy

A large number of current studies and experimental results show that the feedback effect of TCM combined with Western medicine in the treatment of ITP is significantly better than that of the single western medicine group. At the same time, the current treatment of ITP is usually carried out by means of hormone remission and shock therapy, which inevitably leads to some toxic and side

effects and adverse reactions. Through the combination of traditional Chinese and Western medicine treatment, on the one hand, a more ideal therapeutic effect can be obtained; on the other hand, the mild effect of Traditional Chinese medicine can also alleviate some possible side effects and adverse reactions. Bao chapter meter, etc. [36] through blood spirit soup recipe, to Yin deficiency blood hot jump walkers with three groups of patients with clinical syndrome differentiation to agent such as use of compatibility of traditional Chinese medicine treatment, joint for small single dose of glucocorticoid drugs at the same time give the liquid form, syndrome differentiation of traditional Chinese medicine treats joint group syndrome symptoms curative effect for the group total effectiveness 86.67%, not compatibility with Chinese traditional medicine group cure rate to reach 50.00%, The total effective rate of TCM syndrome treatment in the treatment group was also significantly increased, and the adverse reactions were lower than cyclosporine ($P<0.01$). Similar results, the clinical study conducted by Wu Qing et al., with the help of stir-black Gui-pi Decoction, also achieved almost the same good long-term effect, and the PLT level of patients in the combined application of Chinese medicine treatment group was significantly higher than that of the clinical control group ($P<0.05$) [37]. Xu Xiaodu, peng han [38,39] proposed, for the all of the patients with chronic or recurrence in patients with ITP, and refractory with various drugs cause recrudesce ITP, hormone drug dependence caused by all kinds of type secondary ITP patients, with traditional Chinese medicine (TCM) scheme combined the clinical treatment of western medicine, has good effect to improve effect and decrease toxicity [40]. In Han Peng's study, the TCM syndrome score of the observation group was (6.85±1.4) points lower than that of the control group (11.78±3.01) points after the combined treatment of Traditional Chinese and Western medicine, and the syndrome score of the TCM perspective also improved significantly. At the same time, the current Chinese clinic for children on the basis of the drug treatment of ITP virus is currently a hot research topic, such as Yang Xiaoqian, Shao Jingbo, Huang Zhihui people in [43] 41 - through the comparison of different types and cool blood detoxification application analysis found that the effect of [44], compared with the method of the obvious advantages, the hormone group stopped after a week .The recurrence rate was 57.1%, higher than that of hormone + Chinese medicine group (18.%,$P=0.008$). The combination of traditional Chinese and western medicine showed certain advantages in both effect and safety in children.

According to the theory of Traditional Chinese medicine, nourishing Yin and Yang, namely, using hypotenuse, rhubarb [45] and other drugs to supplement Yin and qi, also has guiding significance for ITP patients' rehabilitation [46]. Starting from the theory of cell and molecular, wang tao, Qiu Yingyu thinks, recuperation of traditional Chinese medicines by yiqi huoxue fang, associated with T cell subgroup of recovery, the secretion of cytokines and repair metabolism [47] play a promote and promote role, the basic theory of traditional Chinese medicine combined with clinical treatment of western medicine is a clinical research hotspots at present [48].

ITP is an autoimmune disease, which is manifested by decreased platelet content and associated potential complications. In this paper, the treatment mechanism, clinical treatment means and treatment effect of ITP are sorted out and then appropriate clinical treatment means and treatment suggestions are given to ITP patients at different stages.High-dose corticosteroids are often the first choice for first-line treatment of ITP, which mainly targets patients with early thrombocytopenia. Combined with the latest research progress, it can be found that the combination of drugs in first-line treatment can improve the treatment efficiency, reduce drug resistance of patients, and save the treatment cost. Now common first-line treatment combination with IVIg, drugs to boost platelet production, Ai QuBo palmer ethanolamine, etc., but only 60%-80% of the patients respond to first-line therapy, and mostly in the process of reduction or withdrawal recurrence, thus have to second-line therapy, the common secondary treatment splenectomy, drugs to boost platelet production, rituxan, etc., Second-line therapy is often used for the treatment of chronic thrombocytopenia in clinical practice, with obvious effects and advantages of low recurrence. With the improvement of endoscopic technology and clinical surgical skills, laparoscopic splenectomy (LS) has been gradually praised by experts and scholars for its wide range of application, small tissue damage, good recovery and other advantages. The advance of the surgical process in the course of patients also has great research and practical significance, among which tpo-RA, as a platelet promoting agent, is also the golden key to the second-line treatment of ITP. Recent theoretical studies tend to study the mechanism of Tpo-RA to achieve sustained remission and the classification of action targets. This makes it possible for late clinical use to enable patients to achieve sustained remission while discontinuing medication and avoiding surgery.

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